NDA 20-607/S-005
G.D. Searle & Company
Attention: Mary Jo Pritza, MPH., Pharm.D.
Regulatory Affairs Associate
4901 Searle Parkway
Skokie, IL 60077

OCT 3 2000

Dear Dr. Pritza:

Please refer to your supplemental new drug application dated April 12, 2000, received April 13, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec® (declofenac sodium/misoprostol) Tablets.

This supplemental new drug application provides for revised text and the addition of statements regarding uterine perforation and uterine rupture to the boxed CONTRAINDICATIONS AND WARNINGS, and revised text to the "Geriatric Use" subsection of the PRECAUTIONS section of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted April 12, 2000). Accordingly, the supplemental application is approved effective on October 03, 2000.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 3l4.80 and 3l4.81.

SEARLE

Arthrotec®

(diclofenac sodium and misoprostol)

Tablets

CONTRAINDICATIONS AND WARNINGS

ARTHROTEC (diclofenac sodium/misoprostol) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE ITS MISOPROSTOL COMPONENT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT (See **WARNINGS** and **PRECAUTIONS**).

- Anecdotal reports have been received, primarily from Brazil, of congenital anomalies and reports of fetal death in pregnancies in which misoprostol has been used as an abortifacient.

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED INTRAVAGINALLY IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE FIRST TRIMESTER OF PREGNANCY.

UTERINE PERFORATION HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF COMBINED VAGINAL-AND-ORAL MISOPROSTOL IN PREGNANT WOMEN TO INDUCE ABORTION. IN EACH OF THESE REPORTED CASES, THE GESTATIONAL AGE OF THE PREGNANCIES WAS UNKNOWN.

ARTHROTEC should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID. (See *WARNINGS*). In such patients, ARTHROTEC may be prescribed if the patient:

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin ARTHROTEC only on the second or third day of the next normal menstrual period.

DESCRIPTION

ARTHROTEC is a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E_1 analog. ARTHROTEC oral tablets are white to off-white, round, biconvex and approximately 11 mm in diameter. Each tablet consists of an enteric-coated core containing 50 mg (ARTHROTEC 50) or 75 mg (ARTHROTEC 75) diclofenac sodium surrounded by an outer mantle containing 200 mcg misoprostol.

Diclofenac sodium is a phenylacetic acid derivative that is a white to off-white, virtually odorless, crystalline powder. Diclofenac sodium is freely soluble in methanol, soluble in ethanol and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. Its chemical formula and name are:

$C_{14}H_{10}Cl_2NO_2Na$ [M.W. = 318.14] 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt.

Misoprostol is a water-soluble, viscous liquid that contains approximately equal amounts of two diastereomers. Its chemical formula and name are:

$C_{22}H_{38}O_5$ [M.W. = 382.54] (±)methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.

Inactive ingredients in ARTHROTEC include: colloidal silicon dioxide; crospovidone; hydrogenated castor oil; hydroxypropyl methylcellulose; lactose; magnesium stearate; methacrylic acid copolymer; microcrystalline cellulose; povidone (polyvidone) K-30; sodium hydroxide; starch (corn); talc; triethyl citrate.

CLINICAL PHARMACOLOGY

Pharmacodynamics and pharmacokinetics of diclofenac sodium

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac sodium has shown anti-inflammatory, analgesic and antipyretic properties. The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Diclofenac sodium is completely absorbed from the GI tract after fasting, oral administration. The diclofenac sodium in ARTHROTEC is in a pharmaceutical formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH environment of the duodenum. Only 50% of the absorbed dose is systemically available due to first pass metabolism. Peak plasma levels are achieved in 2 hours (range 1–4 hours), and the area under the plasma concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose proportional and are approximately 1.5 and 2.0 mcg/mL for 50 mg and 75 mg doses, respectively.

Plasma concentrations of diclofenac sodium decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac sodium is reversibly bound to human plasma albumin.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and 35% in the bile.

Conjugates of unchanged diclofenac account for 5–10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20–30% of the dose excreted in the urine and for 10–20% of the dose excreted in the bile.

Conjugates of three other metabolites together account for 10–20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Pharmacodynamics and pharmacokinetics of misoprostol

Misoprostol is a synthetic prostaglandin E_1 analog with gastric antisecretory and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis. A deficiency of prostaglandins within the gastric and duodenal mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by NSAIDs.

Misoprostol can increase bicarbonate and mucus production, but in humans this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to prevent gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor intrinsic factor output.

Effects on gastric acid secretion: Misoprostol, over the range of 50–200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine- and meal-stimulated secretion.

Orally administered misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its biologically active metabolite, misoprostol acid. Misoprostol acid in ARTHROTEC reaches a maximum plasma concentration in about 20 minutes and is, thereafter, quickly eliminated with an elimination $t_{1/2}$ of about 30 minutes. There is high variability in plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose of misoprostol over the range of 200 to 400 mcg. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

After oral administration of radiolabeled misoprostol, about 70% of detected radioactivity appears in the urine. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food, and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid; this effect does not appear to be clinically important.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine or propranolol given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

Pharmacokinetics of ARTHROTEC

The pharmacokinetics following oral administration of a single dose (see Table 1) or multiple doses of ARTHROTEC (diclofenac sodium/misoprostol) to healthy subjects under fasted conditions are similar to the pharmacokinetics of the two individual components.

Table 1.

MISOPROSTOL ACID Mean (SD)			
Treatment (n=36)	C_{max} (pg/mL)	t_{max} (hr)	AUC (0–4h) (pg·hr/mL)
ARTHROTEC 50	441 (137)	0.30 (0.13)	266 (95)
Cytotec®	478 (201)	0.30 (0.10)	295 (143)
ARTHROTEC 75	304 (110)	0.26 (0.09)	177 (49)
Cytotec	390 (130)	0.35 (0.12)	176 (58)

Table 1. *(continued)*

DICLOFENAC Mean (SD)			
Treatment (n=36)	C_{max} (ng/mL)	t_{max} (hr)	AUC (0–12h) (ng·hr/mL)
ARTHROTEC 50	1207 (364)	2.4 (1.0)	1380 (272)
Voltaren®	1298 (441)	2.4 (1.0)	1357 (290)
ARTHROTEC 75	2025 (2005)	2.0 (1.4)	2773 (1347)
Voltaren	2367 (1318)	1.9 (0.7)	2609 (1185)

SD: Standard deviation of the mean
AUC: Area under the curve
C_{max}: Peak concentration
t_{max}: Time to peak concentration

The rate and extent of absorption of both diclofenac sodium and misoprostol acid from ARTHROTEC 50 and ARTHROTEC 75 are similar to those from diclofenac sodium and misoprostol formulations each administered alone.

Neither diclofenac sodium nor misoprostol acid accumulated in plasma following repeated doses of ARTHROTEC given every 12 hours under fasted conditions. Food decreases the multiple-dose bioavailability profile of ARTHROTEC 50 and ARTHROTEC 75.

Special populations

A 4-week study, comparing plasma level profiles of diclofenac (50 mg bid) in younger (26–46 years) versus older (66–81 years) adults, did not show differences between age groups (10 patients per age group). In a multiple-dose (bid) crossover study of 24 people aged 65 years or older, the misoprostol contained in ARTHROTEC did not affect the pharmacokinetics of diclofenac sodium.

Differences in the pharmacokinetics of diclofenac have not been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min), AUC values and elimination rates were comparable to those in healthy people. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy people.

Pharmacokinetic studies with misoprostol in patients with varying degrees of renal impairment showed an approximate doubling of $t_{1/2}$, C_{max} and AUC compared to healthy people. In people over 64 years of age, the AUC for misoprostol acid is increased.

Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme system in animals. In a study of people with mild to moderate hepatic impairment, mean misoprostol acid AUC and C_{max} showed approximately double the mean values obtained in healthy people. Three people who had the lowest antipyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and C_{max} values.

CLINICAL STUDIES

Osteoarthritis

Diclofenac sodium, as a single ingredient or in combination with misoprostol, has been shown to be effective in the management of the signs and symptoms of osteoarthritis.

Rheumatoid arthritis

Diclofenac sodium, as a single ingredient or in combination with misoprostol, has been shown to be effective in the management of the signs and symptoms of rheumatoid arthritis.

Upper gastrointestinal safety

Diclofenac, and other NSAIDs, have caused serious gastrointestinal toxicity, such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine. Misoprostol has been shown to reduce the incidence of endoscopically diagnosed NSAID-induced gastric and duodenal ulcers. In a 12-week, randomized, double-blind, dose response study, misoprostol 200 mcg administered qid, tid or bid, was significantly more effective than placebo in reducing the incidence of gastric ulcer in OA and RA patients using a variety of NSAIDs. The tid regimen was therapeutically equivalent to misoprostol 200 mcg qid with respect to the prevention of gastric ulcers. Misoprostol 200 mcg given bid was less effective than 200 mcg given tid or qid. The incidence of NSAID-induced duodenal ulcer was also significantly reduced with all three regimens of misoprostol compared to placebo (see Table 2).

Table 2.
Misoprostol 200 mcg Dosage Regimen

	Placebo	bid	tid	qid
Gastric ulcer	11%	6%*	3%*	3%*
Duodenal ulcer	6%	2%*	3%*	1%*

N=1623; 12 weeks.
*Misoprostol significantly different from placebo ($p<0.05$)

Results of a study in 572 patients with osteoarthritis demonstrate that patients receiving ARTHROTEC have a lower incidence of endoscopically defined gastric ulcers compared to patients receiving diclofenac sodium (see Table 3).

Table 3.

Osteoarthritis patients with history of ulcer or erosive disease (N=572), 6 weeks	Incidence of ulcers	
	Gastric	Duodenal
ARTHROTEC 50 tid	3%*	6%
ARTHROTEC 75 bid	4%*	3%
diclofenac sodium 75 mg bid	11%	7%
placebo		

*Statistically significantly different from diclofenac ($p<0.05$)

INDICATIONS AND USAGE

ARTHROTEC is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. See *WARNINGS—Gastrointestinal effects* for a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications.

CONTRAINDICATIONS

See boxed ***CONTRAINDICATIONS AND WARNINGS*** related to misoprostol.

ARTHROTEC is contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins. ARTHROTEC should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac sodium have been reported.

WARNINGS

Regarding misoprostol:
See boxed ***CONTRAINDICATIONS AND WARNINGS***.

Regarding diclofenac:

Gastrointestinal (GI) effects—risk of GI ulceration, bleeding and perforation

Serious GI toxicity, such as inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.

Patients should be informed about the signs and/or symptoms and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding, or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3–6 months, and in 2–4% of patients treated for 1 year. These trends continue with increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy has risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** For very high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a history of peptic ulcer disease and/or GI bleeding, and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other conditions or co-therapies that may increase the risk for GI bleeding, such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, older age, smoking, alcoholism, poor general health and *Helicobacter pylori* positive status.

Hepatic effects

Elevations of one or more liver tests may occur during ARTHROTEC therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (ie, less than 3 times the ULN [ULN = the upper limit of the normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (ie, more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open, controlled trial, meaningful elevations of ALT and/or AST occurred in about 4% of 3,700 patients treated for 2–6 months, including marked elevations (ie, more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3–8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

In addition to enzyme elevations seen in clinical trials, postmarketing surveillance has found rare cases of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis with and without jaundice. Some of these rare reported cases underwent liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label) that involved 3,700 patients monitored first at 8 weeks and 1,200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Postmarketing experience has shown severe hepatic reactions can occur at any time during treatment with diclofenac. Cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy. Based on these experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac (see *PRECAUTIONS—Laboratory tests*).

In clinical trials with ARTHROTEC, meaningful elevation of ALT (SGPT, more than 3 times the ULN) occurred in 1.6% of 2,184 patients treated with ARTHROTEC and in 1.4% of 1,691 patients treated with diclofenac sodium. These increases were generally transient, and enzyme levels returned to within the normal range upon discontinuation of ARTHROTEC therapy. The misoprostol component of ARTHROTEC does not appear to exacerbate the hepatic effects caused by the diclofenac sodium component. As with other NSAID containing products, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc), ARTHROTEC should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (eg, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

Anaphylactoid reactions

As with other NSAID containing products, anaphylactoid reactions may occur in patients without known prior exposure to ARTHROTEC or its components. ARTHROTEC should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see *CONTRAINDICATIONS* and *PRECAUTIONS—Preexisting asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs. Allergic reactions have been reported by less than 0.1% of patients who received ARTHROTEC in clinical trials, and there have been rare reports of anaphylaxis in the marketed use of ARTHROTEC outside of the United States.

Advanced renal disease

In patients with advanced kidney disease, treatment with ARTHROTEC is not recommended. If NSAID therapy must be initiated however, close monitoring of the patient's kidney function is advisable (see *PRECAUTIONS—Renal effects*).

PRECAUTIONS

Information for patients

Patients should be advised of the following:

SPECIAL NOTE FOR WOMEN: ARTHROTEC contains misoprostol. Because of its abortifacient property, misoprostol is contraindicated for use by pregnant women. Misoprostol may cause miscarriage if given to pregnant women at any time during pregnancy. Miscarriages caused by misoprostol may be incomplete, which could lead to dangerous bleeding, hospitalization, surgery, infertility, or maternal or fetal death.

See *PATIENT INFORMATION* at the end of this labeling for important information to discuss with the patient.

ARTHROTEC is available only as a unit-of-use package that includes a leaflet containing patient information. The patient should read the leaflet before taking ARTHROTEC and each time the prescription is renewed because the leaflet may have been revised. Keep ARTHROTEC out of the reach of children.

General

ARTHROTEC cannot be used to substitute for corticosteroids or to treat for corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of ARTHROTEC in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

Renal effects

Caution should be used when initiating treatment with ARTHROTEC in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with ARTHROTEC. Caution is also recommended in patients with preexisting kidney disease (see *WARNINGS—Advanced renal disease*).

As with other NSAIDs, long-term administration of diclofenac has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Diclofenac metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematologic effects

Anemia is sometimes seen in patients receiving diclofenac or other NSAIDs. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ARTHROTEC, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs that inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and, unlike aspirin, their effect on platelet function is reversible, quantitatively less, and of shorter duration. ARTHROTEC does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving ARTHROTEC who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Aseptic meningitis

As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of its being related to diclofenac should be considered.

Fluid retention and edema

Fluid retention and edema have been observed in some patients taking NSAID containing products, including ARTHROTEC. Therefore, as with other NSAID containing products, ARTHROTEC should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Preexisting asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-

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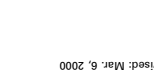

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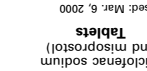

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SEARLE

Arthrotec®

(diclofenac sodium and misoprostol)

Tablets

Revised: Mar. 6, 2000

sensitive patients, ARTHROTEC should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Porphyria

The use of ARTHROTEC in patients with hepatic porphyria should be avoided. To date, one patient has been described in whom diclofenac sodium probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac sodium, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Laboratory tests

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc) or if abnormal liver tests persist or worsen, ARTHROTEC should be discontinued.

Effect on blood coagulation: Diclofenac sodium impairs platelet aggregation but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Diclofenac sodium is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed. Misoprostol has not been shown to exacerbate the effects of diclofenac on platelet activity.

Drug interactions

Aspirin: Concomitant administration of ARTHROTEC and aspirin is not recommended because diclofenac sodium is displaced from its binding sites by aspirin, resulting in lower plasma concentrations, peak plasma levels and AUC values.

Digoxin: Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac sodium. Patients receiving digoxin and ARTHROTEC should be monitored for possible digoxin toxicity.

Antihypertensive agents: NSAIDs can inhibit the activity of antihypertensives, including ACE inhibitors. Thus, caution should be taken when administering ARTHROTEC with such agents.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious bleeding greater than users of either drug alone.

Oral hypoglycemics: Diclofenac sodium does not alter glucose metabolism in healthy people nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experience, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac sodium that necessitated change in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac sodium may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Methotrexate and cyclosporine: ARTHROTEC, like other NSAID containing products, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of ARTHROTEC may increase serum concentrations of methotrexate and increase cyclosporine nephrotoxicity. Patients who begin taking ARTHROTEC or who increase their dose of ARTHROTEC or any other NSAID containing product while taking methotrexate or cyclosporine may develop toxicity characteristic for these drugs. They should be observed closely, particularly if renal function is impaired.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Antacids: Antacids reduce the bioavailability of misoprostol acid. Antacids may also delay absorption of diclofenac sodium. Magnesium-containing antacids exacerbate misoprostol-associated diarrhea. Thus, it is not recommended that ARTHROTEC be coadministered with magnesium-containing antacids.

Diuretics: The diclofenac sodium component of ARTHROTEC, like other NSAIDs, can inhibit the activity of diuretics. Concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other drugs: In small groups of patients (7–10 patients/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline or digitoxin did not significantly affect the peak levels and AUC levels of diclofenac sodium. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy. *In vitro*, diclofenac interferes minimally with the protein binding of prednisolone (10% decrease in binding). Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence, *in vitro*, on the protein binding of diclofenac in human serum.

Animal toxicology

A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse during long-term toxicology studies with misoprostol. No such increase has been observed in humans administered misoprostol for up to 1 year. An apparent response of the female mouse to misoprostol in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.

Carcinogenesis, mutagenesis, impairment of fertility

Long-term animal studies to evaluate the potential for carcinogenesis and animal studies to evaluate the effects on fertility have been performed with each component of ARTHROTEC given alone. ARTHROTEC itself (diclofenac sodium and misoprostol combinations in 250:1 ratio) was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the rat lymphocyte chromosome aberration test or the mouse micronucleus test.

In a 24-month rat carcinogenicity study, oral misoprostol at doses up to 2.4 mg/kg/day (14.4 mg/m^2/day, 24 times the recommended maximum human dose of 0.6 mg/m^2/day) was not tumorigenic. In a 21-month mouse carcinogenicity study, oral misoprostol at doses up to 16 mg/kg/day (48 mg/m^2/day), 80 times the recommended maximum human dose based on body surface area, was not tumorigenic. Misoprostol, when administered to male and female breeding rats in an oral dose-range of 0.1 to 10 mg/kg/day (0.6 to 60 mg/m^2/day, 1 to 100 times the recommended maximum human dose based on body surface area) produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

In a 24-month rat carcinogenicity study, oral diclofenac sodium up to 2 mg/kg/day (12 mg/m^2/day) was not tumorigenic. For a 50-kg person (of average height (1.46m^2 body surface area), this dose represents 0.08 times the recommended maximum human dose (148 mg/m^2) on a body surface area basis. In a 24-month mouse carcinogenicity study, oral diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m^2/day, 0.006 times the recommended maximum human dose based on body surface area) in males and 1 mg/kg/day (3 mg/m^2/day, 0.02 times the recommended maximum human dose based on body surface area) in females was not tumorigenic. Diclofenac sodium at oral doses up to 4 mg/kg/day (24 mg/m^2/day, 0.16 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Pregnancy category X: See boxed ***CONTRAINDICATIONS AND WARNINGS*** regarding misoprostol. One case of amniotic fluid embolism, which resulted in maternal and fetal death, has been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Non-teratogenic effects

Misoprostol may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. Misoprostol produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by misoprostol may be incomplete. In studies in women undergoing elective termination of pregnancy during the first trimester, misoprostol caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%.

Reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to use of misoprostol alone, as an abortifacient, have been received (see boxed ***CONTRAINDICATIONS AND WARNINGS***). If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

The diclofenac sodium component of ARTHROTEC, like other NSAIDs which are prostaglandin-inhibiting drugs, may affect the fetal cardiovascular system causing premature closure of the ductus arteriosus. NSAIDs may also inhibit uterine contractions.

Teratogenic effects

An oral teratology study has been performed in pregnant rabbits at dose combinations (250:1 ratio) up to 10 mg/kg/day diclofenac sodium (120 mg/m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and 0.04 mg/kg/day misoprostol (0.48 mg/m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and has revealed no evidence of teratogenic potential for ARTHROTEC.

Oral teratology studies have been performed in pregnant rats at doses up to 1.6 mg/kg/day (9.6 mg/m^2/day, 16 times the recommended maximum human dose based on body surface area) and pregnant rabbits at doses up to 1.0 mg/kg/day (12 mg/m^2/day, 20 times the recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for misoprostol.

Oral teratology studies have been performed in pregnant mice at doses up to 20 mg/kg/day (60 mg/m^2/day, 0.4 times the recommended maximum human dose based on body surface area), pregnant rats at doses up to 10 mg/kg/day (60 mg/m^2/day, 0.4 times the recommended maximum human dose based on body surface area) and pregnant rabbits at doses up to 10 mg/kg/day (120 mg/m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for diclofenac sodium.

Nursing mothers

Diclofenac sodium has been found in the milk of nursing mothers. It is unlikely that misoprostol is excreted into milk since the drug is rapidly metabolized throughout the body. Excretion of the active metabolite (misoprostol acid) into milk is possible, but has not been studied. Because of the potential for serious adverse reactions in nursing infants, ARTHROTEC is not recommended for use by nursing mothers.

Pediatric use

Safety and effectiveness of ARTHROTEC in pediatric patients have not been established.

Geriatric use

Of the more than 2,100 subjects in clinical studies with ARTHROTEC, 25% were 65 and over, while 6% were 75 and over. In studies with diclofenac, 31% of subjects were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with any NSAID, the elderly are likely to tolerate adverse events less well than younger patients.

Diclofenac is known to be substantially excreted by the kidney, and the risk of toxic reactions to ARTHROTEC may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see *PRECAUTIONS—Renal effects*).

Based on studies in the elderly, no adjustment of the dose of ARTHROTEC is necessary in the elderly for pharmacokinetic reasons (see *Pharmacokinetics of ARTHROTEC—Special populations*), although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging.

ADVERSE REACTIONS

Adverse reactions associated with ARTHROTEC

Adverse reaction information for ARTHROTEC is derived from Phase III multinational controlled clinical trials in over 2,000 patients, receiving ARTHROTEC 50 or ARTHROTEC 75, as well as from blinded, controlled trials of Voltaren® Delayed-Release Tablets (diclofenac) and Cytotec® Tablets (misoprostol).

Gastrointestinal

GI disorders had the highest reported incidence of adverse events for patients receiving ARTHROTEC. These events were generally minor, but led to discontinuation of therapy in 9% of patients on ARTHROTEC and 5% of patients on diclofenac. For GI ulcer rates, see *CLINICAL STUDIES—Upper gastrointestinal safety.*

GI disorder	ARTHROTEC	Diclofenac
Abdominal pain	21%	15%
Diarrhea	19%	11%
Dyspepsia	14%	11%
Nausea	11%	6%
Flatulence	9%	4%

ARTHROTEC can cause more abdominal pain, diarrhea and other GI symptoms than diclofenac alone.

Diarrhea and abdominal pain developed early in the course of therapy, and were usually self-limited (resolved after 2 to 7 days). Rare instances of profound diarrhea leading to severe dehydration have been reported in patients receiving misoprostol. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if ARTHROTEC is prescribed. The incidence of diarrhea can be minimized by administering ARTHROTEC with food and by avoiding coadministration with magnesium-containing antacids.

Gynecological

Gynecological disorders previously reported with misoprostol use have also been reported for women receiving ARTHROTEC (see below). Postmenopausal vaginal bleeding may be related to ARTHROTEC administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. There have been reports in which intravaginal administration of misoprostol in pregnant women resulted in rupture of the uterus and death of the infant. (See boxed ***CONTRAINDICATIONS AND WARNINGS***.)

Elderly

Overall, there were no significant differences in the safety profile of ARTHROTEC in over 500 patients 65 years of age or older compared with younger patients.

Other adverse experiences reported occasionally or rarely with ARTHROTEC, diclofenac or other NSAIDs, or misoprostol are:

Body as a whole: Asthenia, death, fatigue, fever, infection, malaise, sepsis.

Cardiovascular system: Arrhythmia, atrial fibrillation, congestive heart failure, hypertension, hypotension, increased CPK, increased LDH, myocardial infarction, palpitations, phlebitis, premature ventricular contractions, syncope, tachycardia, vasculitis.

Central and peripheral nervous system: Coma, convulsions, dizziness, drowsiness, headache, hyperesthesia, hypertonia, hypoesthesia, insomnia, meningitis, migraine, neuralgia, paresthesia, somnolence, tremor, vertigo.

Digestive: Anorexia, appetite changes, constipation, dry mouth, dysphagia, enteritis, esophageal ulceration, esophagitis, eructation, gastritis, gastroesophageal reflux, GI bleeding, GI neoplasm benign, glossitis, heartburn, hematemesis, hemorrhoids, intestinal perforation, peptic ulcer, stomatitis and ulcerative stomatitis, tenesmus, vomiting.

Female reproductive disorders: Breast pain, dysmenorrhea, intermenstrual bleeding, leukorrhea, menstrual disorder, menorrhagia, vaginal hemorrhage.

Hemic and lymphatic system: Agranulocytosis, anemia, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, lymphadenopathy, melena, pancytopenia, pulmonary embolism, purpura, rectal bleeding, thrombocythemia, thrombocytopenia.

Hypersensitivity: Angioedema, laryngeal/pharyngeal edema, urticaria.

Liver and biliary system: Abnormal hepatic function, bilirubinemia, hepatitis, jaundice, liver failure, pancreatitis.

Male reproductive disorders: Impotence, perineal pain.

Metabolic and nutritional: Alkaline phosphatase increased, BUN increased, dehydration, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hyponatremia, periorbital edema, porphyria, weight changes.

Musculoskeletal system: Arthralgia, myalgia.

Psychiatric: Anxiety, concentration impaired, confusion, depression, disorientation, dream abnormalities, hallucinations, irritability, nervousness, paranoia, psychotic reaction.

Respiratory system: Asthma, coughing, dyspnea, hyperventilation, pneumonia, respiratory depression.

Skin and appendages: Acne, alopecia, bruising, eczema, erythema multiforme, exfoliative dermatitis, hemophigoid reaction, photosensitivity, pruritus, pruritus ani, rash, skin ulceration, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis.

Special senses: Hearing impairment, taste loss, taste perversion, tinnitus.

Urinary system: Cystitis, dysuria, hematuria, interstitial nephritis, micturition frequency, nocturia, nephrotic syndrome, oliguria/polyuria, papillary necrosis, proteinuria, renal failure, urinary tract infection.

Vision: Amblyopia, blurred vision, conjunctivitis, diplopia, glaucoma, iritis, lacrimation abnormal, night blindness, vision abnormal.

OVERDOSAGE

The toxic dose of ARTHROTEC has not been determined. However, signs of overdosage from the components of the product have been described.

Diclofenac sodium

Clinical signs that may suggest diclofenac sodium overdose include GI complaints, confusion, drowsiness or general hypotonia. Reports of overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old man who suffered loss of consciousness, increased intracranial pressure, and aspiration pneumonitis, and died 2 days after overdose. A 24-year-old woman who took 4.0 g and the 28- and 42-year-old women, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal studies show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg: rats, 55; dogs, 500; monkeys, 3200).

Misoprostol

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of GI discomfort being reported. In animals, the acute toxic effects are diarrhea, GI lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia.

ARTHROTEC

Symptoms of ARTHROTEC overdosage should be treated with supportive therapy. In case of acute overdosage, gastric lavage is recommended. Induced diuresis may be beneficial because diclofenac sodium and misoprostol metabolites are excreted in the urine. The effect of dialysis or hemoperfusion on the elimination of diclofenac sodium (99% protein bound) and misoprostol acid remains unproven. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol.

DOSAGE AND ADMINISTRATION

ARTHROTEC is administered as ARTHROTEC 50 (50 mg diclofenac sodium/200 mcg misoprostol) or as ARTHROTEC 75 (75 mg diclofenac sodium/200 mcg misoprostol).

Note: See *SPECIAL DOSING CONSIDERATIONS* section, below.

Osteoarthritis: The recommended dosage for maximal GI mucosal protection is ARTHROTEC 50 tid. For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers. This fixed combination product, ARTHROTEC, is not appropriate for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

	OA regimen	Diclofenac sodium (mg/day)	Misoprostol (mcg/day)
ARTHROTEC 50	tid	150	600
	bid	100	400
ARTHROTEC 75	bid	150	400

Rheumatoid Arthritis: The recommended dosage is ARTHROTEC 50 tid or qid. For patients who experience intolerance, ARTHROTEC 75 bid or ARTHROTEC 50 bid can be used, but are less effective in preventing ulcers. This fixed combination product, ARTHROTEC, is not appropriate for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

	RA regimen	Diclofenac sodium (mg/day)	Misoprostol (mcg/day)
ARTHROTEC 50	qid	200	800
	tid	150	600
	bid	100	400
ARTHROTEC 75	bid	150	400

SPECIAL DOSING CONSIDERATIONS: ARTHROTEC contains misoprostol, which provides protection against gastric and duodenal ulcers (see *CLINICAL STUDIES*). For gastric ulcer prevention, the 200 mcg qid and tid regimens are therapeutically equivalent, but more protective than the bid regimen. For duodenal ulcer prevention, the qid regimen is more protective than the tid or bid regimens. However, the qid regimen is less well tolerated than the tid regimen because of usually self-limited diarrhea related to the misoprostol dose (see *ADVERSE REACTIONS—Gastrointestinal*), and the bid regimen may be better tolerated than tid in some patients.

Dosages may be individualized using the separate products (misoprostol and diclofenac), after which the patient may be changed to the appropriate ARTHROTEC dose. If clinically indicated, misoprostol co-therapy with ARTHROTEC, or use of the individual components to optimize the misoprostol dose and/or frequency of administration, may be appropriate. The total dose of misoprostol should not exceed 800 mcg/day, and no more than 200 mcg of misoprostol should be administered at any one time. Doses of diclofenac higher than 150 mg/day in osteoarthritis or higher than 225 mg/day in rheumatoid arthritis are not recommended.

For additional information, it may be helpful to refer to the package inserts for Cytotec® tablets and Voltaren® tablets.

HOW SUPPLIED

ARTHROTEC (diclofenac sodium/misoprostol) is supplied as a film-coated tablet in dosage strengths of either 50 mg diclofenac sodium/200 mcg misoprostol or 75 mg diclofenac sodium/200 mcg misoprostol. The 50 mg/200 mcg dosage strength is a round, biconvex, white to off-white tablet imprinted with four "A's" encircling a "50" in the middle on one side and "SEARLE" and "1411" on the other. The 75 mg/200 mcg dosage strength is a round, biconvex, white to off-white tablet imprinted with four "A's" encircling a "75" in the middle on one side and "SEARLE" and "1421" on the other.

The dosage strengths are supplied in:

Strength	NDC Number	Size
50/200	0025–1411–60	bottle of 60
	0025–1411–90	bottle of 90
	0025–1411–34	carton of 100 unit dose
75/200	0025–1421–60	bottle of 60
	0025–1421–34	carton of 100 unit dose

Store at or below 25°C (77°F), in a dry area.

PATIENT INFORMATION

Read this leaflet before taking ARTHROTEC (diclofenac sodium 50 or 75 mg/misoprostol 200 mcg) and each time your prescription is renewed, because the leaflet may be changed.

ARTHROTEC is being prescribed by your doctor for treatment of your arthritis symptoms while at the same time providing protection from the development of stomach and intestinal ulcers due to the arthritis medication. ARTHROTEC contains diclofenac, an arthritis medication. ARTHROTEC also contains misoprostol to decrease the chance of getting stomach and intestinal ulcers that sometimes develop with NSAID medications. Serious side effects are still possible, however, and you should report to your physician any signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain or swelling. If signs of liver toxicity occur (nausea, fatigue, lethargy, itching, jaundice, right upper quadrant tenderness, and "flu-like" symptoms) you should stop therapy and seek immediate medical attention.

Do not take ARTHROTEC if you are pregnant, because it contains misoprostol which can cause miscarriage if given at any stage of pregnancy. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Misoprostol may cause the uterus to rupture (tear) in pregnant women if it is used to bring on (induce) labor or to cause an abortion after the first trimester of pregnancy. Miscarriages or rupture of the uterus may result in severe bleeding, hospitalization, surgery, infertility or death.

If you become pregnant during ARTHROTEC therapy, stop taking ARTHROTEC and contact your doctor immediately. Remember that even if you are using a means of birth control, it is still possible to become pregnant. Should this occur, stop taking ARTHROTEC and consult your physician immediately.

ARTHROTEC may cause diarrhea, abdominal pain, upset stomach and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week with continued treatment. You can minimize possible diarrhea by making sure you take ARTHROTEC with meals and by avoiding the use of antacids containing magnesium (if needed, use one containing aluminum or calcium instead). ARTHROTEC tablets should be swallowed whole, and not chewed, crushed or dissolved.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take ARTHROTEC. If you have prolonged difficulty (more than 7 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take ARTHROTEC only according to the directions given by your doctor. Changes in dose should be made only with your doctor's approval.

Do not give ARTHROTEC to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and could be dangerous for another person, especially a woman who may be, or could become, pregnant.

This information sheet does not cover all possible side effects of ARTHROTEC. See your doctor if you have questions.

Keep out of reach of children.

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Tablets

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